Full Text HL-96-015

MOLECULAR BIOLOGY AND GENETICS OF SLEEP AND SLEEP DISORDERS

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National Heart, Lung, and Blood Institute
National Institute on Mental Health
National Institute on Child Health and Human Development

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THIS RFA USES "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS AND INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS AND MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS RFA.

PURPOSE

The purpose of this initiative is to advance our understanding of the molecular and genetic basis of sleep and sleep disorders. Specifically, the program is designed to stimulate studies on basic molecular correlates of sleep, cellular mechanisms responsible for restorative processes during sleep, the interactions between sleep and circadian systems controlling sleep and wakefulness at a molecular level, the genetic basis of sleep disorders, and the molecular neurobiology of sleep and sleep disorders.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This request for applications (RFA), Molecular Biology and Genetics of Sleep and Sleep Disorders, is related to the priority areas of heart disease and stroke, chronic disabling conditions, mental health and disorders, maternal and infant health, and clinical prevention services. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal Government. Foreign institutions may not apply. However, subcontracts to foreign institutions maybe allowed if justified. Ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

Collaborations and consortia promoting the cross-fertilization of ideas are strongly encouraged. In such cases, each participant's contribution should be identified and well-integrated into the overall experimental design.

MECHANISM OF SUPPORT

This RFA will use the NIH individual research project grant (R01) mechanism of support. Awards will be made and managed by the National Heart, Lung, and Blood Institute (NHLBI) and/or the National Institute of Mental Health (NIMH) and/or the National Institute on Child Health and Human Development (NICHD). Policies that govern the research grants programs of the NIH will prevail. However, specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by the NIH. The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, applicant institutions, reviewers, and Institute staff.

For this RFA, funds must be requested in $25,000 direct cost modules and a maximum of 9 modules ($225,000 direct costs) per year may be requested. A feature of the modular grant concept is that no escalation is provided for future years, and all anticipated expenses for all years of the project must be included within the number of modules being requested. Only limited budget information will be required and any budget adjustments made by the Initial Review Group will be in modules of $25,000. Instructions for completing the Biographical Sketch have also been modified. In addition, Other Support information and the application Checklist page are not required as part of the initial application. If there is a possibility for an award, necessary budget, Other Support and Checklist information will be requested by staff at NHLBI and/or NIMH and/or NICHD following the initial review. The APPLICATION PROCEDURES section of this RFA provides specific details of these modifications to standard PHS 398 application kit instructions.

This RFA is a one time solicitation. Future unsolicited competing continuation applications will compete with all investigator initiated applications and be reviewed according to customary peer review procedures.

FUNDS AVAILABLE

It is anticipated that during fiscal year 1997, support will be available for total costs of approximately $2,000,000 from the NHLBI, $800,000 from NIMH, and $400,000 from NICHD for the first year of this initiative. Award of grants pursuant to this RFA is contingent upon receipt of such funds for this purpose. It is anticipated that approximately 12 to 15 grants will be awarded under this program. Applicants may request up to four years of support. The specific number to be funded will, however, depend on the merit and scope of the applications received and on the availability of funds. Direct costs will be awarded in modules of $25,000, less any overlap or other necessary administrative adjustments. Indirect costs will be awarded based on the negotiated rates.

RESEARCH OBJECTIVES

Background

Sleep related problems represent a significant health concern for millions of Americans and all age groups. The impact of sleep disturbances on society includes reduced productivity, lowered cognitive performance, increased likelihood of accidents, decreased quality of life, and higher risk of morbidity and mortality. Sleep disturbances are important markers of affective disorders and possibly are a contributing factor in the pathogenesis of Sudden Infant Death Syndrome.

Although recent scientific progress has provided a strong foundation for advancing our basic scientific understanding of this important clinical problem, neurobiological mechanisms underlying normal and disordered sleep remain largely unknown. Physiological, metabolic, and behavioral processes during sleep contribute to the normal function and maturation of the nervous system. Improved understanding of how sleep modifies the nervous system at a molecular level is critical to develop new approaches for the primary prevention and treatment of sleep disorders.

Research Scope

Little is currently known about the molecular events involved in sleep regulation or the restorative processes that occur in neurons and/or glia during sleep. Consequently, there are a number of directions that could be pursued by applicants responding to this RFA. The topics that follow serve as examples and are not a comprehensive or exclusive list of the areas supported by this initiative. Applicants are encouraged to propose other topics consistent with the goals of this program. An essential requirement of this RFA is that the framework for proposed studies include molecular or genetic approaches.

A current hypothesis is that sleep-promoting compounds accumulate during wakefulness and are dissipated during sleep. Although a number of candidate compounds have been proposed, the study of these compounds needs to be extended to a molecular level. For instance, we need to know whether molecular events leading to the formation of sleep promoting molecules or their receptors are regulated by the sleep/wake cycle and how this regulation is achieved in relevant brain regions.

Defining the basic role of sleep in health and disease represents a significant, unmet biological challenge. One theory is that sleep has a restorative role such as replenishing the energy stores of glia or contributing to the reorganization of synaptic connections. Molecular studies to test these hypotheses are strongly encouraged. A related question is whether molecular changes in brain function accompany sleep deprivation. Sleep deprivation may have long-term effects through changes in gene expression (e.g. IL-1beta, TNF, and prostaglandins) and neuronal plasticity. Where are these genes regulated (cell type, location) and what signals account for changes in transcriptional regulation? Studies are also needed to identify the role of specific sleep regulating molecules that provoke the development of major affective disorders or are linked to cardiorespiratory or thermoregulatory function.

Animal models are needed to study the development and maintenance of neuronal circuitry controlling sleep (e.g. synaptogenesis, neural plasticity) using molecular techniques. The mouse

provides an especially useful vehicle for studying homeostatic control of sleep because techniques are available to precisely manipulate gene expression in this species. The role of specific genes in sleep disorders could be investigated using knock-out, knock-in, and other recently developed transgenic techniques in mouse models.

Current definitions of sleep are based primarily on criteria derived from the mammalian electroencephalogram and hence limit the study of sleep to mammalian species. However, the genome of nonmammalian species (e.g., Drosophila, C. Elegans) is more easily manipulated and presents the opportunity to develop model systems in which the basic control mechanisms governing activity cycles and their effects on neurobiological processes can be investigated. The development of new approaches enabling the neurobiological significance of sleep to be studied in nonmammalian species is encouraged.

There are significant changes to the sleep process that occur across the life span. The neurobiological basis for such changes and especially the role of sleep regulating molecules in development and aging requires investigation. Animal models containing specific gene deletions may have unique value for studying the molecular basis for altered patterns of sleep and rhythmicity associated with development or traumatic experiences. Studies are also needed to determine whether neurodegenerative mechanisms (e.g., apoptosis) or molecular defects in neuroendocrine regulation are factors in the pathogenesis of sleep disorders with age.

Genetic factors are implicated in many sleep disorders, e.g., narcolepsy, restless legs syndrome (RLS) and obstructive sleep apnea (OSA). Narcolepsy is associated with an HLA subtype and close relatives of individuals with narcolepsy have a much greater risk of having the disorder. Studies are needed in human narcolepsy to advance our understanding of fundamental sleep mechanisms and open new areas of investigation. Narcolepsy in a canine model of the disorder is transmitted as a single autosomal recessive trait. However, genetic studies in the canine model have been hampered by the lack of information on the canine genome. On the other hand, a large base of genetic information is available in mice. The development of a mouse model of narcolepsy would advance markedly studies of this disease and create new opportunities to investigate the genetic basis for sleep disorders. In this regard, genetic factors are also thought to contribute significantly to restless leg syndrome (RLS) and obstructive sleep apnea (OSA) since multiple family members are frequently affected when one of these disorders is present. In the case of OSA, familial risk seems to be associated with certain facial bony structures suggesting that the genes determining that structure are involved. A close familial association may also exist with respect to primary insomnia. Studies contributing a more precise definition of the genetic basis for these and other sleep disorders including elements associated with

behavioral and mental disorders and genetic disorders affecting arousal and cardiorespiratory or thermoregulatory function during sleep and infancy will be responsive.

SPECIAL REQUIREMENTS

The primary focus of proposed studies must be on the molecular or genetic basis of sleep and sleep disorders. Studies of the circadian system must be tightly coupled to mechanisms of sleep control. Psychobiological, neurophysiological, anatomical, or polysomnographic studies which do not include molecular or genetic approaches to understanding sleep will be considered unresponsive to this RFA. Pharmacological studies that investigate the efficacy of sleep promoting agents but not the underlying molecular mechanisms will also not be acceptable. Studies proposing the use of nonmammalian species should clearly establish the relationship of these models to the goals set forth in this RFA. Applicants are encouraged to contact the program officials listed under INQUIRIES for further information.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minorities in Study Populations), which have been in effect since 1990. The policy contains some provisions that are substantially different from the 1990 policies. All investigators proposing research involving human subjects should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994, (F 59 14508-14513), and reprinted in the NIH GUIDE FOR GRANTS AND CONTRACTS of March 18, 1994, Volume 23, Number 11.

Investigators may obtain copies of the policy from these sources or from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

LETTER OF INTENT

Prospective applicants are asked to submit, by January 6, 1997, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel, participating institutions, and the number and title of the RFA in response to which the application may be submitted.

Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains allows NIH staff to estimate the potential review workload and to avoid conflict of interest in the review. The letter of intent is to be faxed or sent to Dr. C. James Scheirer, at the address listed under INQUIRIES.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev. 5/95). Applications kits are available at most institutional offices of sponsored research and may be obtained from the Grants Information Office, Office of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: ASKNIH@odrockm1.od.nih.gov.

The RFA label available in the PHS 398 application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, to identify the application as a response to this RFA, check "YES" in item 2 of page 1 of the application and enter the title "Molecular Biology and Genetics of Sleep and Sleep Disorders, HL-96-015".

The following modifications are made to the standard PHS 398 application instructions:

BUDGET INSTRUCTIONS

The total direct costs must be requested in accordance with the program guidelines and modifications made to the standard PHS 398 application instructions as described below:

o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD - Do not complete Form Page 4 of the PHS 398 (rev 5/95). It is not required nor will it be accepted at the time of application.

o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget tables on Form page 5 of the PHS 398 (rev. 5/95). Only the requested total

direct costs line for each year must be completed based on the number of $25,000 modules being requested. Applicants may not request a change in the amount of each module. A maximum of 9 modules ($225,000 direct costs) per year may be requested and each applicant may request up to four years of support for this RFA. Direct cost budget remain constant throughout the life of the project (i.e., the same number of modules requested for all budget periods). Any necessary escalation should be considered when determining the number of modules to be requested. However, in the event that the number of modules requested must change in any future year due to the nature of the research proposed, appropriate justification must be provided. Total Direct Costs for the Entire Proposed Project Period should be shown in the box provided.

o BUDGET JUSTIFICATION

- Budget justifications should be provided under "Justifications" on Form Page 5 of the PHS 398.
- List the names, role on the project and proposed percent effort for all project personnel (salaried or unsalaried) and provide a narrative justification for each person based on his/her role on the project.
- Identify all consultants by name and organizational affiliation and describe the services to be performed.
-Provide a general narrative justification for individual categories (equipment, supplies, etc.) required to complete the work proposed.

More detailed justifications should be provided for high cost items.

Any large one-time purchases, such as large equipment requests, must be accommodated within these limits.

o CONSORTIUM/CONTRACTUAL COSTS - If collaborations or subcontracts are involved that require transfer of funds from the grantee to other institutions, it is necessary to establish formal subcontract agreements with each collaborating institution. A letter of intent from each collaborating institution should be submitted with the application. Only the percentage of the consortium/contractual TOTAL COSTS (direct and indirect) relative to the total DIRECT COSTS of the overall project needs to be stated at this time. The following example should be used to indicate the percentage cost of the consortium, "The consortium agreement represents 27% of overall $175,000 direct costs requested in the first year". A budget justification for the consortium should be provided as described in the "Budget Justification" section above (no Form Page 5 required for the consortium). Please indicate whether the consortium will be in place for the entire project period and identify any future year changes in the percentage relative to the parent grant.

If there is a possibility for an award, the applicant will be requested to identify actual direct and indirect costs for all years of the consortium. Please note that total subcontract costs need not be calculated in $25,000 modules. However, when subcontract funds are added to the parent grant budget, the total direct cost amount must be included in the number of $25,000 modules requested.

o BIOGRAPHICAL SKETCH - Biographical sketches are required for key personnel, following the modified instructions below. Do not exceed the two-page limit for each person.
- Complete the educational block at the top of the form page;
- List current position(s) and those previous positions directly relevant to the application;
- List selected peer-reviewed publications directly relevant to the proposed project, with full citation;
- The applicant has the option to provide information on research projects completed and/or research grants participated in during the last five years that are relevant to the proposed project.

o OTHER SUPPORT - Do not complete the "Other Support" pages (Form Page 7). Selected other support information relevant to the proposed research may be included in the Biographical Sketch as indicated above. Complete Other Support information will be requested by the staff of NHLBI or collaborating Institutes if there is a possibility for an award.

o CHECKLIST - No "Checklist" page is required as part of the initial application. A completed Checklist will be requested by the staff of NHLBI or collaborating Institutes if there is a possibility for an award.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

Applications not conforming to these guidelines will be considered unresponsive to this RFA and will be returned without further review.

Submit a signed, typewritten original of the application and three signed, photocopies, in one package to:

DIVISION OF RESEARCH GRANTS
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710

BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application must be sent to Dr. C. James Scheirer, at the address listed under INQUIRIES.

Applications must be received by March 13, 1997. If an application is received after this date, it will be returned to the applicant without review. The Division of Research Grants (DRG) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The DRG will also not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

o A sample budget is available upon request from Mr. Raymond Zimmerman at the number listed under INQUIRIES.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the DRG and responsiveness to this RFA by the collaborating institutes. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration. Applications will be evaluated for scientific and technical merit by an appropriate peer review group convened by the Division of Extramural Affairs, NHLBI.

As part of the initial merit review, all applications will receive a written critique and undergo a review in which only those applications deemed to have the highest scientific merit of the applications under review (usually two to three times the number of applications that the NHLBI and participating Institutes anticipate being able to fund under the program) will be discussed, assigned a priority score, and receive a second level review by the National Heart, Lung, and Blood Advisory Council and the Advisory Council of NIMH and/or NICHD.

The following criteria will be considered when assessing the scientific and technical merit of a research grant application:

o Scientific, technical, or medical significance and originality of proposed research.

o Appropriateness and adequacy of the experimental approach and methodology.

o Qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research. Applications that couple basic sleep with molecular biology or genetics expertise are strongly encouraged.

o Availability of the resources necessary to perform the research.

The personnel category will be reviewed for appropriate staffing based on the requested percent effort. The direct costs budget request will be reviewed for consistency with the proposed methods and specific aims. Any budgetary adjustments recommended by the reviewers will be in $25,000 modules. The duration of support will be reviewed to determine if it is appropriate to ensure successful completion of the requested scope of the project.

AWARD CRITERIA

The anticipated date of award is September 30, 1997. Factors that will be taken into consideration in making awards include the scientific merit of the proposed program as evidenced by the priority score and the availability of funds. Subject to the availability of necessary funds and consonant with the priorities of this RFA, the NHLBI, NIMH, and/or NICHD will provide funds for a project period up to four years.

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

James P. Kiley, Ph.D.
National Center on Sleep Disorders Research
National Heart, Lung, Blood Institute
6701 Rockledge Drive, Suite 7024, MSC-7920
Bethesda, MD 20892-7920
Telephone: (301) 435-0199
FAX: (301) 480-3451
Email: Kileyj@nih.gov

Israel I. Lederhendler, Ph.D.
Coordinator for Sleep Research
National Institute of Mental Health
5600 Fishers Lane, Room 11-102
Rockville, MD 20857
Telephone: (301) 443-1576
FAX: (301) 443-4822
Email: ilu@helix.nih.gov

Marian Willinger, Ph.D.
Pregnancy and Perinatology Branch
National Institute of Child Health and Human Development
6100 Executive Boulevard, Room 4B03
Bethesda, MD 20892
Telephone: (301) 496-5575
Email: willingm@hd01.nichd.nih.gov

Direct inquiries regarding review matters to:

C. James Scheirer, Ph.D.
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
6701 Rockledge Drive, Room 7220, MSC 7924
Bethesda, MD 20892-7924
Telephone: (301) 435-0266
FAX: (301) 480-3541
Email: ScheireJ@nih.gov

Direct inquiries regarding fiscal matters to:

Raymond L. Zimmerman
Grants Operations Branch
National Heart, Lung, and Blood Institute
6701 Rockledge Drive, Room 7154
Bethesda, MD 20892-7926
Telephone: (301) 435-0171
FAX: (301) 480-3310

Email: ZimmermR@nih.gov

Diana Trunnell
Grants Management Branch
National Institute of Mental Health
5600 Fishers Lane, Room 7C-08
Rockville, MD 20857
Telephone: (301) 443-3065
Email: dt21a@nih.gov

Douglas Shawver
Office of Grants and Contracts
National Institute of Child Health and Human Development
6100 Executive Boulevard, Room 8A17
Bethesda, MD 20892
Telephone: (301) 496-1303
Email: shawverd@hd01.nichd.nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.838. Grants are made under the authorization of the Public Health Service Act, Title III, Section 301 (Public Law 78-410, as amended by Public Law 99-158, 42 US 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is subject to the intergovernmental review requirements of Executive Order 12372 or to a review by a Health Systems Agency.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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